

COMBAT Bladder Cancer with Hyperthermia



COMBAT BRS Bladder Recirculation System



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The COMBAT BRS delivers heated chemotherapy, HIVEC® (Hyperthermic Intra-Vesical Chemotherapy), to optimise the chemotherapy treatment for NMIBC patients.

The COMBAT BRS is a closed, conductive, recirculation system with accurate temperature control that ensures homogenous heated drug distribution.

HIVEC® real world data shows promising results for reducing recurrence and progression rates in certain patient groups. 867 patients are currently in randomised controlled HIVEC® trials. Results from these trials are expected to be consistent with the evidence being seen in the real world data published to date.



Innovation

The COMBAT BRS delivers homogenous drug and heat distribution to maximise chemotherapeutic and hyperthermic benefit and treatment outcomes.

Utilising an external, dry, conductive recirculation method, the innovative and patented aluminum heat exchanger ensures efficient heat transfer and accurate temperature control within ± 0.2 of set temperature.

Integration

Simple to integrate into current clinical practice, the COMBAT BRS is portable, robust and easy to use.

It requires minimal set-up without continuous monitoring, allowing for multiple simultaneous treatments by a single clinician. System and kit are affordable and reimbursed in an expanding number of countries. As clinical evidence grows we continue to show cost savings for the healthcare provider through improved patient outcomes.

Combination

Hyperthermia has been shown to significantly increase the effectiveness of Mitomycin C (MMC) in NMIBC^{1,2}.

The mutually enhancing effects of chemotherapy in combination with hyperthermia have been well documented for their cytotoxic effects. Chemo-Hyperthermia (CHT) is widely used in the treatment of several types of cancer including bladder cancer³.

Our dedicated clinical and product team are supporting in the integration of the COMBAT BRS into hospitals in a growing number of countries.

"HIVEC® offers a new treatment option for patients with high and intermediate risk bladder cancer. For patients where BCG is not tolerated, not available, or has failed, HIVEC® offers a promising well tolerated alternative bladder preserving treatment in selected patients."

Mr D Wilby | Consultant Urologist Portsmouth Hospitals NHS Trust

Why use Hyperthermia to treat NMIBC?

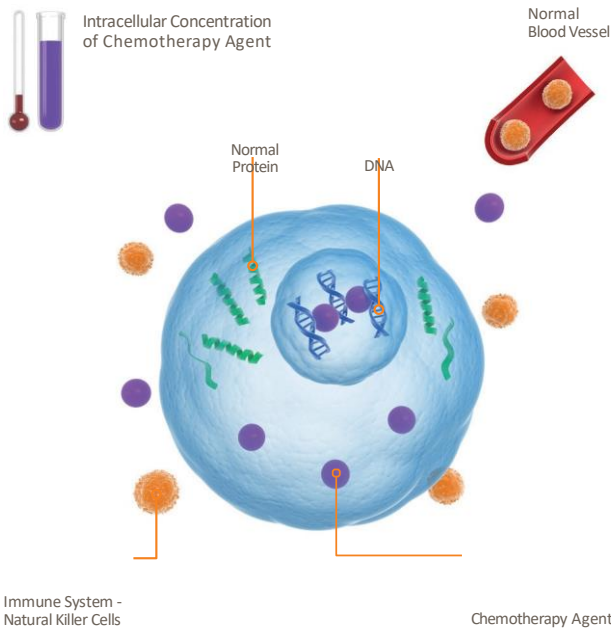
Clinical hyperthermia is defined as the therapeutic use of temperature between 41°C to 44°C. The introduction of thermal energy affects the cancer cells more because of their inability to manage the heat as well as healthy cells. Mitomycin C (MMC) is stable at temperatures up to 50°C, but has shown to be **1.4 times more active at 43°C**. Hyperthermia **inhibits the formation of new blood vessels** (angiogenesis) by the tumour mass. At 43°C the **cytotoxicity increases by 10 times**, without any increase in the toxicity to the patient. At elevated temperatures the lipid-protein cellular membrane bilayer will become more permeable, due to the unfolding (denaturing) of the cellular membrane and cytosolic proteins. These resulting in **higher intracellular concentration of the chemotherapy agent**. Direct effects on the DNA include; **strand breaking, impaired transcription, reducing replication and cell division**. **Thermotherapy has profound effects on the immune system** resulting in **increased activation of more natural killer cells** (NKC) that target heat stressed cancer cells as they signal heat shock proteins on the cancer cell surface. The consequence is that the cancer cells actively participate in their own demise through the natural process of **apoptosis**.

Chemo-hyperthermia multifactorial modes of action create a strong combination effect, ensuring cancer tumours and cells are specifically targeted. **Therefore hyperthermia substantially increases the effectiveness of chemotherapy compared to instillation at room temperature**. The **COMBAT BRS** is the **first system** to allow the delivery of thermotherapy within the tight parameters necessary **to optimise the delivery of chemo-hyperthermia without compromising patient safety, comfort or increasing resources required**.

Based on the available body of evidence including real world experience data, the recommended protocol to achieve best results with HIVEC® for intermediate patients is a 6 weekly induction treatment plus an additional 1 year maintenance for High Risk patients.

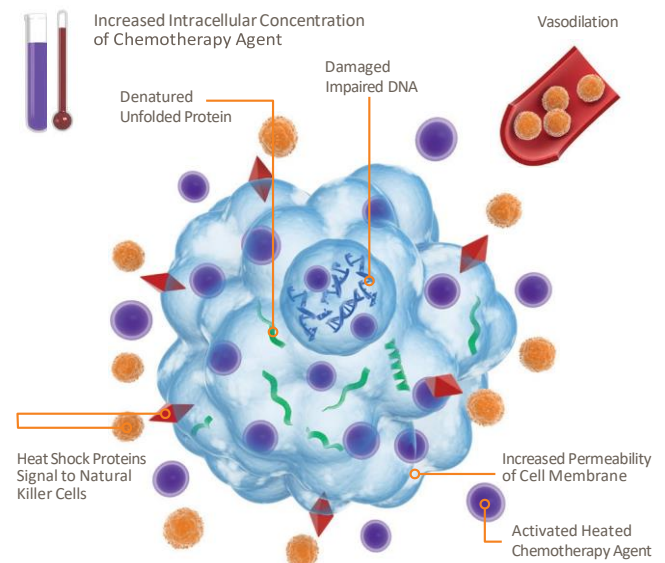
Cancer cell with Mitomycin C Delivered at room temperature

Normothermia



Cancer cell with Mitomycin C Delivered at 43°C

Hyperthermia

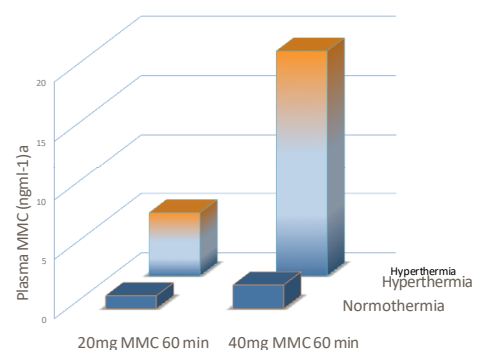


Effect of hyperthermia on alkylating agents Teicher et al (1981) demonstrated activation rates 1.3 – 1.4 times higher at 41°C, 42°C, and 43°C compared to 37°C.

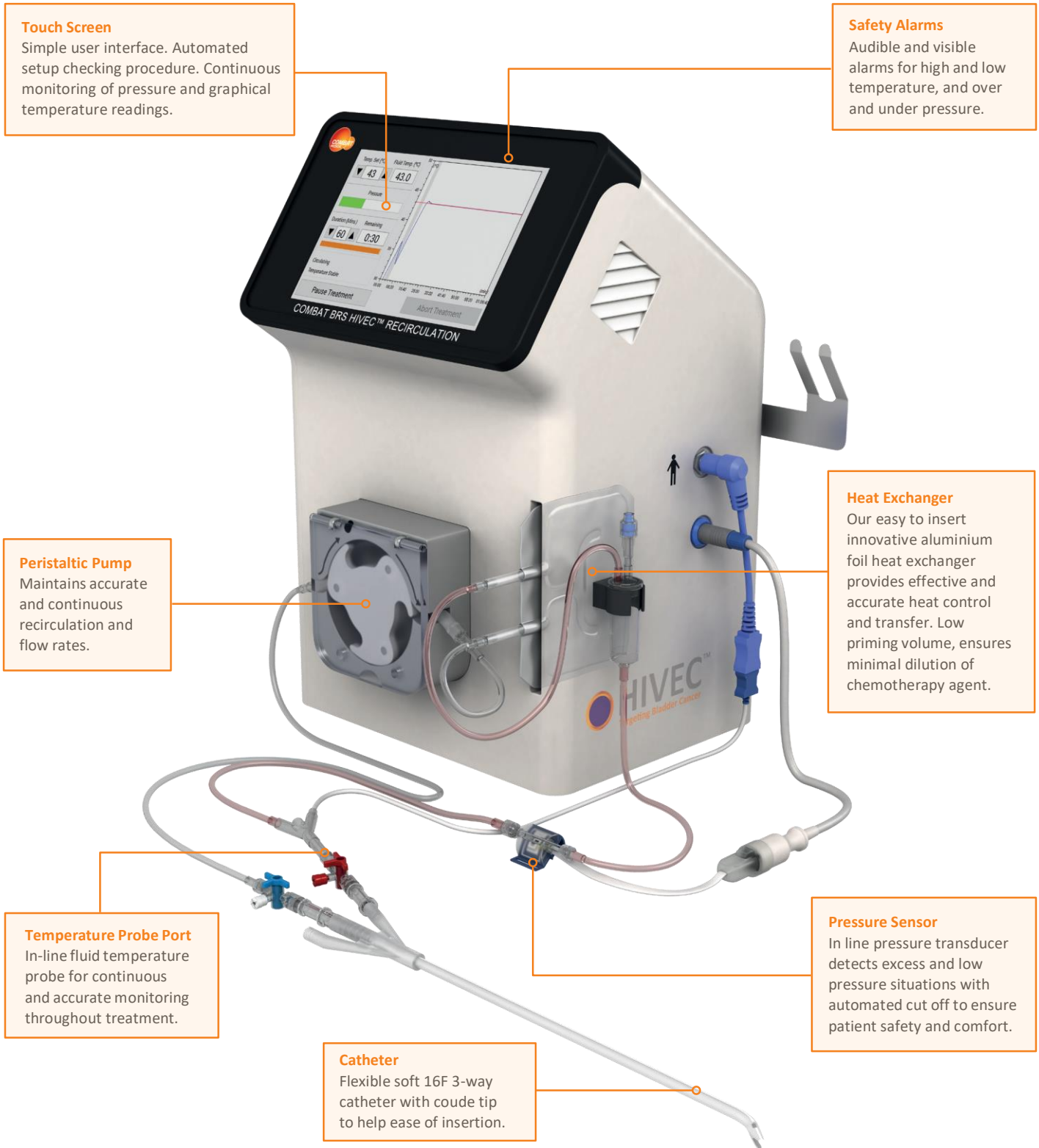
Mitomycin C remains stable at higher temperatures.						
Temp.	Solvent	Parameter	Storage Period			
			0 hr*	1 hr	3 hr	6 hr
37°C	5 ml water	Content %	100.0	94.9	92.8	91.6
	5 ml of saline	Content %	100.0	94.2	90.6	90.4
50°C	5 ml water	Content %	100.0	91.0	88.0	87.3
	5 ml of saline	Content %	100.0	91.3	90.2	89.7

*0 hr : immediately after reconstitution.

Mitomycin C (MMC) plus hyperthermia achieves greater plasma concentration than MMC alone, but is well below 400ng/ml associated with systemic side effects like myelosuppression.



The **COMBAT BRS** and its unique patented features for enhanced usability and patient comfort in the delivery of **HIVEC®** for NMIBC treatment.



Touch Screen

Simple user interface. Automated setup checking procedure. Continuous monitoring of pressure and graphical temperature readings.

Safety Alarms

Audible and visible alarms for high and low temperature, and over and under pressure.

Peristaltic Pump

Maintains accurate and continuous recirculation and flow rates.

Heat Exchanger

Our easy to insert innovative aluminium foil heat exchanger provides effective and accurate heat control and transfer. Low priming volume, ensures minimal dilution of chemotherapy agent.

Temperature Probe Port

In-line fluid temperature probe for continuous and accurate monitoring throughout treatment.

Pressure Sensor

In line pressure transducer detects excess and low pressure situations with automated cut off to ensure patient safety and comfort.

Catheter

Flexible soft 16F 3-way catheter with coude tip to help ease of insertion.

The Key Benefits of the COMBAT BRS for delivering HIVEC®

Technical

"Our mission is to drive change in order to optimise the efficacy of the conventional chemotherapy instillation. Reducing recurrence and progression rates in Non-Muscle Invasive Bladder Cancer in a cost effective way that fits alongside current practices."

Edward Bruce-White
COMBAT Medical CEO

Increased Efficacy

Uniform Heating and Drug Distribution

The COMBAT BRS ensures accurate and even heat control, drug distribution and optimal hyperthermic benefit.

The chemotherapy is dissolved as in standard practice and then recirculated through a closed system via a 3 way catheter. Evidence shows HIVEC® delivery by the COMBAT BRS achieves a consistent intravesical temperature of 42.90°C (± 0.14) effectively heating the entire bladder wall⁴.

By recirculating low fluid volumes through the patented heat exchanger it provides consistent and accurate heated chemotherapy with no ineffective hot or cold spots or up to 40% superficial burns as have been reported in alternative RF microwave heating methods¹.

Accurate Temperature Control

It has been proven that the COMBAT BRS accurately heats at set temperature (± 0.14)⁴. Operating within tightly controlled parameters in hyperthermic drug delivery is important for patient safety and optimisation of hyperthermic benefit.

Temperatures lower than 39°C are ineffective and temperatures higher than 43.5°C can lead to decreased blood perfusion due to vascular collapse and in turn result in poorer drug delivery⁵. Temperatures higher than 45°C can lead to increased toxicity and patient discomfort.

It is widely considered that the optimal temperature for intravesical hyperthermia is 43°C

The COMBAT BRS accurately measures temperature, showing constant graphical readings on its touch screen for ease of use and reassurance for the healthcare provider. No other hyperthermia system has proven evidence to show it can accurately control the heat within the tight parameters required.

Increased Patient Comfort and Tolerability

Lower Pressure and Fluid Volume

The innovative patented aluminum heat exchanger allows for maximum heat efficiency and uniformity. Importantly, this efficiency means that flow rates and pressure levels are kept low when the system is in use. The **low flow rates and pressure levels** make it easier for the patient to tolerate and remain comfortable during treatment. This makes **treatment completion rates for HIVEC® delivered by the COMBAT BRS, similar to those of standard chemotherapy treatment**⁶.

Small Catheter

The COMBAT catheter is the **smallest of any hyperthermia systems**. Our soft, 16Fr catheter with a coude tip is designed to aid easy insertion and increase patient comfort.

Recently presented interim safety and tolerability data from the HIVEC I & II trials found **no statistical difference between reported side effects in the HIVEC® or passive MMC groups**.

This indicates that our catheter carries a **similar safety and comfort profile to catheters used in standard Intravesical therapy**⁶.

Summary:

- Uniform heating for homogenous heat distribution throughout the bladder⁴. No areas left untreated and no hot or cold spots that can result in tolerability issues³.
- Easy and accurate temperature control that does not require continuous operator involvement. Ensures safety and treatment optimisation.
- Scalable system, easy to integrate into existing practice.
- Flow rates and pressure levels kept low during treatment for patient comfort and tolerability.
- Small catheter resulting in fewer reported side effects, less patient discomfort and higher number of successfully completed treatments⁶.

COMBAT continues to invest in clinical trials while increasing its real world evidence to prove its efficacy in the treatment of NMIBC.

Clinical

Tolerability:

The unique technical advantages of the COMBAT BRS result in a favorable patient tolerability profile as demonstrated by the recent publication of HIVEC® I & II interim tolerability data:

The tolerability data presented at the 32nd EAU meeting in 2017 summarised the results drawn from **307 patients**, from 25 Spanish and UK hospitals, with a mean follow up of 12 months⁶.

There was a similarly **high level of completed treatments** in both the HIVEC® (88.9%) and Mitomycin (94.8%) groups, with drug allergy being the main reason for stopping in both arms⁶.

There was **no statistical difference** in **adverse events (AE)** between the HIVEC® and Cold Mitomycin arms with most of the reported AEs being grade II or lower⁶.

There was no difference between the HIVEC® and standard Mitomycin arms with respect to pain, dysuria, urgency, incontinence, nocturia, UTIs or rashes; in addition, **no urethral strictures** were reported in either of the treatment arms⁶.

The conclusion of the interim data was that:

“HIVEC® treatment represents a safe and well tolerated intravesical treatment for NMIBC”⁶.

Efficacy:

The first efficacy data from our HIVEC I & II trials is due in 2019. As experience and usage grows, clinicians globally are publishing and presenting their efficacy data as it becomes available. Data has recently been presented at all the major urology congresses. For further details and copies of all evidence please contact us.

High Risk and CIS:

A retrospective analysis of 145 HR NMIBC patients treated with HIVEC® in 14 centers across Europe, due to BCG unavailability or patient intolerance presented at AUA 2018⁷.

All patients received a minimum of 6 weekly installations with a variable maintenance schedule. **The median follow up was 21 months, recurrence free rate (RFR) was 82% and progression free rate (PFR) was 98%⁷.**

The study concluded that CHT with 6 weekly induction, 40mg MMC using the **COMBAT BRS, represents an attractive alternative to intravesical BCG therapy** while acknowledging that randomised controlled trials are eagerly awaited⁷.

Further results presented in 2018 in BCG unresponsive patients unwilling or unfit for radical cystectomies concluded that HIVEC® is a valid treatment option in BCG unresponsive intermediate or high-risk patients, potentially avoiding or postponing the need for radical surgery in these patients⁸.

Over 500 patients real world efficacy data and over 300 patients safety and tolerability data presented and published over the last 5 years.

Full copies of all abstracts and publications presented are available on our website or contact us directly.

"In light of the BCG crisis, HIVEC® was the treatment of choice by our trust in Leicestershire in continuing to manage the fight against High Risk Non Muscle Invasive Bladder Cancer for our patients. The COMBAT BRS is efficient, user friendly and has proven to be a pioneering treatment delivery system that's well tolerated by patients."

Michelle Brewster | Urology Clinical Nurse
Specialist, Leicestershire Hospitals
NHS Trust

High Risk and CIS - A Sequential Regime:

In response to the Global BCG shortage, TRL Griffiths et al, Leicester University Hospital, devised a treatment schedule incorporating sequential HIVEC® and BCG instillations to treat high risk patients. Patients received a total of 15 instillations (12 HIVEC®TM, 3 BCG) over a 6-weekly induction followed by 1 year maintenance schedule⁹.

Data presented at AUA 2017 outlined the 1 year follow up of a 50 HR patient cohort (CIS detected in 40% and T1 in 62%) treated with this regime. It showed that 88% of patients were disease free and 86% of patients tolerated treatments very well⁹.

A recent review of the 2 year follow up data showed that 47 (94%) were progression free, 46 (92%) cystectomy free and 38 (76%) disease free. 84% tolerated the complete treatment schedule.

TRL Griffiths et al concluded that the expected results are at least comparative with expected results for BCG maintenance with very promising tolerability and compliance rates. They found the low progression and good tolerability at the 2 year stage reassuring⁹.

Intermediate Risk:

In a recent publication Sousa et al assessed the use of both Adjuvant and Neoadjuvant HIVEC® in Intermediate and High-Risk patients, with encouraging results¹⁰.

The results demonstrated that within the Neoadjuvant group (who received 80mg in 50ml x 8 weekly instillations prior to TURBT), 62.5% had a complete response at the time of the planned TUR, with a further 33.3% experiencing a partial response of >50% reduction in tumour size. The four-year recurrence rate for this group was 20.8%¹⁰.

Within the Adjuvant group (who received 4 x weekly and then 6 x monthly instillations of 40mg in 40ml), the reported recurrence rate at 2 years was 12.5%, which compares favorably to the standard expected recurrence rate for this group of 38% at 1 year¹⁰.

Future:

HIVEC® treatment is currently being used in 5 ongoing trials with 867 NMIBC patients. 3 of these trials with 648 patients have completed clinical recruitment. COMBAT has initiated a further series of trials due to be announced soon.

867 patients currently in HIVEC® trials with the COMBAT BRS. Further series of High Risk trials to be announced. Over 500 patients' real world efficacy data has been presented.

COMBAT provides the following:

- Several multinational multicenter randomised clinical trials in Europe (UK & Spain).
- HIVEC E – a real world data registry sponsored by COMBAT controlled by a designated DMC.
- Dedicated HIVEC website www.hivec.co.uk.
- Patient Information.
- Technical and Product support.

For further information on clinical data release and our clinical trial program please visit our website www.bioargo.com, or contact us directly on: vendas@bioargo.com.

Technical Specifications:

Physical characteristics COMBAT BRS V5

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Equipment external dimensions:

Height 400 mm Width 250 mm Depth 255 mm

Equipment weight:

BRS system 8 Kg plus optional portable stand

Safety alarms:

High & Low temperature alarms

High & Low pressure alarms

Auto safety cut off

End of treatment alarm & auto stop

Electrical risk classification:

Class I, Type B

Fluid ingress protection:

IPX2

Function mode:

Continuous delivery at set temperature between 41 – 44°C ± 0.2°C

Certification:

IEC/UL 60601 - 1; IEC 60601 - 1 - 2; EN 55011; CAN/CSA - C22.2; CE 0086

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